claims 21-22 is found in the specification at page 2, lines 20-24.

Claims 3-5, 7, and 10-11 have been amended to change the dependency of the claims from cancelled claim 19 to new claim 21.

The Examiner has maintained his rejection of pending claims 3-5, 7, 10 and 19-20 under 35 U.S.C. §§ 102 and 103 and contends that the claimed (-)-enantiomer is included within the known (±) mixture. The Examiner has not accepted applicants' arguments that the claimed compounds possess unexpectedly high antiviral activity and low toxicity, stating that "[n]o declaration to that effect is noted in the record here".

Applicants submit herewith the Declaration of Dr. Richard Storer under 37 C.F.R. § 1.132 (the "Storer Decl."). In this Declaration, Dr. Storer, a coinventor of the subject matter described in this application and an expert in the area of antiviral nucleosides, identifies the state of the art at the filing date of this invention (Storer Decl., para. 4-6). Dr. Storer explains why one of skill in the art would have not expected that the (-)-enantiomer of this invention would be as active as its (+)-counterpart, and more particularly, why the remarkably high therapeutic index of the (-)-enantiomer was a completely surprising and valuable discovery (Storer Decl., para. 7-8).

The Declaration of Dr. Storer supports applicants' position that the claimed compounds of this invention possess unexpected and surprisingly improved properties over the generic disclosures of prior art. As an improvement or selection invention, the claimed compounds satisfy the requirements of patentability. Accordingly, applicants request that the Examiner withdraw the rejection under 35 U.S.C. §§ 102 and 103.

The Examiner has rejected claims 19 and 20 under 35 U.S.C. § 112, first and second paragraph. The Examiner has objected to the term "pharmaceutically acceptable derivatives" recited in the claims. Applicants have amended claims 19 and 20 to replace the term "pharmaceutically acceptable derivative thereof" with "pharmaceutically acceptable salt, ester, or salt of such ester thereof, or any other compound which, upon administration to a recipient, is capable of providing *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or an antivirally active metabolite or residue thereof".

The amended claim language, particularly when read in light of the specification, clearly identifies the compounds which fall within the scope of the claims. One of skill in the art would easily recognize whether a compound is a salt, ester, or salt of an ester of *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Similarly, one of skill in the art would readily be able to determine whether a compound becomes cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or an antivirally active metabolite or residue thereof, upon administration to a recipient. Further, the specification provides a list of the preferred pharmaceutically acceptable derivatives within the scope of the present invention at page 2, line 33 to page 3, line 28 of the specification. Applicants, therefore, request that the Examiner withdraw the rejection under 35 U.S.C § 112.

The Examiner has rejected claims 3-5, 7, 10 and 19-20 under 35 U.S.C. §§ 102 and 103 as being unpatentable over United States patents 5,047,407 and 5,204,466. The Examiner's rejection is based on two contentions. First, the Examiner states that "mixtures of (+) [and] (-) enantiomers are still

claimed here". Second, the Examiner contends that the "compound claimed here is known".

In United States patent 5,047,407, the Examiner has specifically highlighted the racemate of the claimed (-)-enantiomer (referred to as compound XII) and a claim to all optical isomers of that compound. In United States patent 5,204,466, the Examiner has specifically highlighted the same racemate (referred to as BCH-189) and noted a reference to "enantiomerically enriched".

Applicants traverse.

First, the mixtures claimed by applicants are patentable over either the '407 or '466 patent. The greater than or equal to 95% enantiomerically pure form of the (-)-enantiomer recited in claim 3 posseses surprising antiviral activity and superior therapeutic index much like the pure (-)-enantiomer (Storer Decl., para 9). Therefore, the 95% pure mixture of claim 3 is patentable over the racemic mixture for the same reasons the pure(-)-enantiomer is patentable.

Second, neither of the cited patents discloses or suggests the potent antiviral activity of the (-)-enantiomer of this invention. Nor is there any description or suggestion of the unexpectedly superior therapeutic index of the (-)-enantiomer in either of the cited patents. Further, as the accompanying Declaration of Dr. Storer demonstrates, one of skill in the art would have supposed that the "enantiomerically enriched" mixtures referred to in United States patent 5,204,466 are enriched in the "natural" (+)-enantiomeric form (Storer Decl. para. 10-12). Because United States patent 5,204,466 never identifies the specific enantiomer that enriches its "enantiomerically enriched BCH-189" it actually teaches away from applicants' invention by implying that, as one of skill in

the art would expect, BCH-189 is enriched with the natural (+)-enantiomer. In fact, it is clear from the specification that the patentee does not even appreciate the surprising activity profile of the two enantiomeric forms of BCH-189. See column 3, lines 53-56: "there exists a need for a stereoselective synthetic route to enantiomerically-enriched ß-BCH-189 because the other enantiomer is inactive and, therefore, represents a 50% impurity" (emphasis added). Thus, a person skilled in the art at the filing date of the present application, would conclude after reading United States patent 5,204,466 that the (-)-enantiomer of BCH-189 is an inactive impurity. Accordingly, applicants request that the Examiner withdraw the rejection under 35 U.S.C. §§ 102 and 103.

Applicants again note that the Examiner has not returned an initialized copy of PTO form 1449, submitted by applicants on September 18, 1992. Applicants have attached a duplicate copy of that document and a copy of the postcard receipt as evidence that the document was received at the United States Patent Office on September 24, 1992. Applicants request that the Examiner return an initialized copy of PTO form 1449 acknowledging his consideration of the cited art.

Respectfully submitted,

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